

REMARKS

Reconsideration and allowance are requested.

Claims 1, 3, 5-16 and 21-26 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. Support for the specific monomers may be found, inter alia, at paragraph [0016] of the specification.

Information Disclosure Statement

To satisfy their continuing duties of candor and good faith, Applicants bring to the Examiner's attention the following related applications having Serial Nos. 10/333,468, 10/333,473, 10/544,541, 10/544,542, 10/546,275, 10/567,728, 11/587,427, 11/885,222 and 11/885,246. He is invited to consider their prosecution histories and prior art, which are accessible through the PTO's Image File Wrapper (IFW), in view of the Federal Circuit's holding in *McKesson Information Solutions v. Bridge Medical*, 82 USPQ2d 1865 (Fed. Cir. 2007). To avoid duplication of those materials in the PTO's records, reference to the IFW is encouraged but Applicants would be ready to submit copies of these materials for the Examiner's review if he prefers.

Consideration of the Information Disclosure Statement filed December 2, 2009 is also requested.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1, 3, 5-16, 21-24 and 26 were rejected under Section 112, first paragraph, because allegedly the specification "does not reasonably provide enablement for any polymer that changes its hydration force as broadly claimed." Applicants traverse. The

present amendments and the teachings in their specification enable the skilled artisan to practice the claimed invention using polymer obtained by polymerization (e.g., homo- or co-polymerization) of one or more monomers selected from the group consisting of (meth)acrylamide compounds, N- (or N,N-di)alkyl-substituted (meth)acrylamide derivatives, and vinyl ether derivatives.

It was alleged on page 4 of the Office Action that the only polymer taught in the specification and art to change hydration force in the temperature range of 0-80°C is poly(N-isopropylacrylamide). A portion of this objection is mooted by amendment of claim 1. Additionally, the polymer is required to be the product of polymerization of one or more monomers selected from the group consisting of (meth)acrylamide compounds, N- (or N,N-di)alkyl-substituted (meth)acrylamide derivatives, and vinyl ether derivatives. It may be a homo- or co-polymer. Support for this amendment is found, inter alia, at paragraph [0016] of the specification. Further limitation of the polymer is unjustified.

On page 5 of the Office Action, it was further alleged that the non-human animal must be immunocompromised because human cancer cells would be attacked by the immune system. It would be incorrect to assume that the claimed invention is limited to human cancer cells. As acknowledged by the Examiner, an immunocompromised non-human animal may be used as a host for human cancer cells. But the cancer cells to be used in Applicants' invention are not limited to those derived from a human being. It is stated in paragraph [0014] of the specification, "The cells to be used in the invention can be derived from various sources that include but are by no means limited to human being, dog, cat, rabbit, rat, swine and sheep." Thus, the claimed invention also encompasses cancer cells obtained from a non-human animal that are transplanted into an animal of the same species (e.g., the case where cancer cells derived from a rat are transplanted into a non-immunocompromised rat).

It was alleged that if the animal is not immunocompromised, "the cancer cells will be attacked by the host's immune system, be destroyed and fail to create a tumor." But if an animal from which the cancer cells are derived and an animal into which the cancer cells are transplanted are of the same species, rejection of the related species would not be expected to be as strong as for unrelated species. If the cancer cells are from an animal of the same species as the animal receiving a transplant of the cancer cells,

Applicants teach that the sheet of cancer cells is successfully transplanted (see paragraph [0007]). Further, the size and/or shape of the cancer tissue in the animal could be controlled by preparing a sheet of cancer cells in a specified size and/or shape (see paragraph [0007] of the present specification).

Finally, given the Examiner's conclusion on page 3 of the Office Action that a cell culture support coated with poly(N-isopropylacrylamide) is enabled, it is submitted that claims 11 and 24 should not have been rejected. Applicant request clarification from the Examiner of the basis for rejecting claims 11 and 24 if this rejection is maintained.

An object of Applicants' claimed invention is to provide a non-human animal free from the problems of the prior art (see paragraph [0004]). Thus, once a novel and non-obvious sheet of cancer cells is provided, conventional techniques may be used to select a non-human animal to receive the transplant, where the sheet will survive until selecting of an anti-tumor agent. Limitation of the non-human animal to a nude mouse is unjustified.

Similarly, the non-human animal made by Applicants' claimed invention could be used in selecting of an anti-tumor agent without undue experimentation. It was alleged on page 6 of the Office Action that "specific steps of administering agents, the controls or how to compare the results so that agents that treat cancer are identified" would require undue experimentation. Such techniques would be known to the skilled artisan. Therefore, if this rejection is maintained, the Examiner is respectfully requested to cite evidence or reasoning that the skilled artisan could not utilize conventional techniques to select anti-tumor agents using Applicants' non-human animal.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 112 – Definiteness

Claims 1, 3, 5-16, 21-24 and 26 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The limitation that the polymer “changes its hydration force in a temperature range of 0-80°C” is deleted from claim 1 because it is not required for patentability. But changes in a polymer’s hydration force can be determined in the temperature range of 0-80°C as taught by paragraphs [0015] and [0016] of the specification. From Applicants’ teachings, the meanings of weak and strong hydration forces are defined in terms of the polymer’s hydration.

The lack of antecedent basis for the cancer tissue in claim 3 is corrected.

It was alleged on page 9 of the Office Action that all cancer cell lines are transplantable. This is not correct. All cancer cell lines are not necessarily transplantable. For example, the phrase “nude mouse transplantable human cancer cell lines” (emphasis added) is found at page 785, column 1, line 22, of Koezuka et al. If all cancer cell lines were transplantable, the term “transplantable” would not have been used because its use would be redundant as it would not have modified the human cancer cell lines. In addition, the sentence “Neither transplantability in nude mice nor colony formation on soft agar was observed, except in one subline” is found in the abstract at lines 13-14 of Ichinose et al. (Jpn. J. Cancer Res., 89:516-524, 1998). Neither transplantability in nude mice nor colony formation on soft agar was observed, except in one subline. Therefore, the objection to the term “transplantable” in claim 6 should be withdrawn because a cancer cell line may be either transplantable or untransplantable.

Similarly, the objection to “untransplantable” in claim 7 should also be withdrawn. Untransplantable cell lines are taught in paragraph [0014] of the specification; MGF-40, MGT-90, CS-C9 and CS-C20 are exemplified as such cell lines.

The skilled artisan could easily distinguish transplantable cell lines from those that are not transplantable. Both types are known in the art and taught in Applicants’ specification. Limiting the cancer cells to specific ones that are either transplantable or untransplantable is not justified because an infringer could then practice the claimed invention by using cell lines other than those taught in the present specification.

As regards claim 9, Applicants do not require “the cancer cells are collected from once living tissue” (emphasis added) but only that they are collected from a living tissue. It is evident from “a living tissue” that the tissue is living when cancer cells are collected.

Not all cancer cells would satisfy this requirement because they could be collected from tissue that is no longer living at present.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1, 4-7, 9 and 12-13 were rejected under Section 102(b) as allegedly anticipated by Koezuka (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994). Applicants traverse.

Koezuka discloses describes a method for culturing human cancer cells by using a thermoresponsive polymer (PNIPAAm) and dextran sulfate. But Applicants' claimed invention greatly differ from Koezuka's disclosure because the prior art requires use of trypsin when the cultured cancer cells are detached from a substrate. Further, Koezuka states that collagen on the substrate, selection medium containing dextran sulfate, and EGTA treatment are indispensable conditions for satisfactory attachment and detachment of cancer cells from the cell culture support. By contrast, the Applicants' claimed invention does not require collagen, dextran sulfate, or EGTA for its process. Instead, the present invention produces satisfactory attachment and detachment of cancer cells from the cell culture support without requiring collagen, dextran sulfate, or EGTA.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d

1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See *id.* (“Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue”). The use of hindsight reasoning is impermissible. See *id.* at 1397 (“A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning”). Thus, a *prima facie* case of obviousness requires “some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct.” *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.* But a claim that is directed to a combination of prior art elements “is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *Id.* Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1, 3, 5-13, 15-16, 21-24 and 26 were rejected under Section 103(a) as allegedly unpatentable over Koezuka (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994) in view of Sakai (JP 05/192138). Applicants traverse.

As explained above, a difference between Applicants’ claimed invention and the prior art (e.g., Koezuka) is that while trypsin or a collagen-coated substrate, a selection medium containing dextran sulfate, and EGTA treatment are indispensable for Koezuka, they are unnecessary for the present invention. One of ordinary skill in the art would have understood from Koezuka’s disclosure that a collagen-coated substrate, selection medium containing dextran sulfate, and EGTA must be used for achieving satisfactory detachment of cancer cells if no trypsin was used. Thus, there would have been no reasonable expectation of success to satisfactorily detach cancer cells from a cell culture support without using trypsin if the collagen-coated substrate, selection medium containing dextran sulfate, and EGTA were not used.

In light of the foregoing, Koezuka teaches away from Applicants' invention and shows a lack of a reasonable expectation of success to make the claimed invention. For the same reasons, the claimed invention is patentability over Koezuka in view of Sakai, which does not address the deficiencies of the primary reference. As taught in paragraph [0004] of the specification, transplanted cancer cells obtained by prior art techniques have poor "take" and the size and weight of the transplanted sheet of cancer cells varies so greatly from one animal to another that evaluation of various anti-cancer agents to reveal any significant differences in their efficacy is difficult.

The object of the present invention is to provide a new non-human animal model free from the problems of the prior art (see paragraph [0004] of the specification). The present invention is characterized in that cancer cells can be transplanted efficiently by using a sheet of cancer cells. Such efficient transplantation of cancer cells into a non-human animal could not been achieved using prior art techniques (see paragraph [0007] of the specification).

The present invention has made it possible to obtain a non-human animal model in which size and/or shape of cancer tissue in the animal can be controlled by preparing a sheet of the cancer cells in a specified size and/or shape. Neither Koezuka nor Sakai would have made the claimed process obvious at the time Applicants' invention was made. In conclusion, the present invention would not have been obvious with a reasonable expectation of success by even a skilled artisan from the combination of Koezuka and Sakai.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.


Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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